

Pharmacotherapeutic Aspects of Space Medicine

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Medications are used for a wide variety of indications during space flight. For example, astronauts have taken drugs in flight to ameliorate or prevent symptoms of space motion sickness, headache, sleeplessness, backache, nasal congestion, and constipation. Russian cosmonauts reportedly take medications to prevent metabolic disturbances of the myocardium and intestinal flora, and to optimize their work capacity. Although the discomfort associated with some acute responses to microgravity (e.g., space motion sickness) is expected to diminish with length of time in flight, other responses that have delayed onset (e.g., maintaining nutritional status, bone and muscle strength, and perhaps immune response) may affect health and quality of life during longer missions. Therefore, as the duration of space flights increases, the need for treatment with medications is expected to increase accordingly.

Medications carried on Space Shuttle missions have varied somewhat from flight to flight, depending on the individual needs of the crewmembers. Medications use during Shuttle flights seems to be more prevalent than during earlier programs, perhaps because drugs are provided in easy-to-use forms. In fact, nearly all medications taken to date have been ingested orally in tablet form. However, given that the oral route may not be ideal for those suffering motion-sickness symptoms, intramuscular and intranasal preparations are being tested. For example, intramuscular administration of promethazine hydrochloride (Phenergan[®]) has been reported to be more effective in alleviating motion-sickness symptoms. The difficulties involved in conducting definitive studies of drug efficacy during U.S. space flights have been compounded by the absence of a systematic approach to determining which drugs were taken by whom and under what circumstances.

The use of some drugs in space has been less efficacious than expected. The onset, intensity, and duration of the response produced by any drug depend upon rates of absorption, distribution, metabolism, and elimination of the drug; space flight-induced changes in blood flow and the function of the gastrointestinal (GI) tract, liver, or kidneys may alter these processes. Another important aspect of clinical efficacy of medications in space is the stability of pharmaceuticals. As the U.S. space program is moving toward extended Space Shuttle flights and beyond, to space station missions and planetary explorations, understanding how space flight affects organ systems and clinical pharmacology is necessary to optimize pharmacotherapeutics in space and ensure adequate safety and health of crewmembers.

The goal of pharmacotherapeutics research at the Johnson Space Center is to provide safe and effective diagnostic and pharmacological intervention products, procedures and strategies in support of successful space medical operations. To achieve this overall goal, research objectives conceived are to: 1) Identify physiologic, pharmacokinetic and pharmacodynamic changes in space; 2) Develop safe and effective non-invasive sustained-release dosage forms and regimens for pharmacological interventions in space, and; 3) Create and maintain a comprehensive space pharmacokinetic, pharmacodynamic and therapeutic database.

Because the physiologic effects of microgravity develop over hours, days, or weeks, it is to be expected that the effects of some medications will change with increasing time spent in space. It should be possible, at least in principle, to assess some of these changes under experimental conditions on Earth. To be significant for space medicine, however, in-flight trials must take place, with replications before and after flight on Earth, in order to assess variations within and between individuals. In view of the heavy workload of flight crews and the present difficulties of performing meaningful pharmacokinetic-pharmacodynamic assessments with humans in space, serious thought should be given to in-flight animal experiments, with concurrent Earth-based controls. Another important aspect of pharmacotherapeutics research should concentrate on the development of therapeutic drug monitoring and chronic drug delivery technologies that can meet the challenges of remote treatment needs for the Space Station and exploration-class missions, *e.g.*, to the moon and Mars.

In classic ground-based pharmacokinetic studies, estimates of the rates of absorption, distribution, metabolism, and excretion of compounds are calculated from measuring the amount of the drug and its metabolites in plasma as a function of time. Logistical problems (*e.g.*, lack of refrigerated storage, difficulty drawing blood in microgravity), as well as the desire to minimize the number of invasive procedures that the astronauts must undergo, have led to efforts to develop less invasive means such as salivary drug monitoring to examine the fate of drugs in the body.

Although much is known about the processes that constitute the pharmacokinetic characteristics of drugs on Earth, including the molecular basis of xenobiotic transport and biotransformation, much less is known about the mechanisms by which drugs elicit their effects, whether desired or adverse. This lack of knowledge severely limits the ability to predict the pharmacodynamic changes that may occur during space flight. Because changes in the dose-response relationship can be caused by changes in pharmacokinetics, pharmacodynamics, or both, data must be obtained to delineate the dose-concentration from the concentration-effect components. Other potential sources of response-variation include stress, lack of sleep, and changes in chronophysiologic status. This implies the need for in-flight assessment of therapeutic response and optimization of dosage regimens based on that response.

Concurrent with noninvasive pharmacokinetic/pharmacodynamic methods development and assessment, design and development of alternatives to enteral dosage forms are also pursued. Data currently available suggest that space flight affects absorption of orally administered medications and stability of drug formulations. These findings support the need for the development of novel drug delivery systems for acute and chronic treatment in space.

In conclusion, optimization of therapeutics for space exploration requires research and development of enabling technologies and methods for the diagnosis and treatment of acute and chronic ailments encountered by astronauts while in space and upon return to Earth.